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Oral Antidiabetic Agents
A Guide to Selection

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Contents

Summary

Type 2 diabetes mellitus (formerly named non–insulin-dependent diabetes mellitus or NIDDM) is a heterogeneous disease resulting from a dynamic interaction between defects in insulin secretion and insulin action. Various pharmacological approaches can be used to improve glucose homeostasis via different modes of action: sulphonylureas essentially stimulate insulin secretion, biguanides (metformin) act by promoting glucose utilisation and reducing hepatic glucose production, α-glucosidase inhibitors (acarbose) slow down carbohydrate absorption from the gut and thiazolidinediones (troglitazone) enhance cellular insulin action on glucose and lipid metabolism.

These pharmacological treatments may be used individually for certain types of patients, or may be combined in a stepwise fashion to provide more ideal glycaemic control for most patients. Selection of oral antihyperglycaemic agents as first-line drug or combined therapy should be based on both the pharmacological properties of the compounds (efficacy and safety profile) and the clinical characteristics of the patient (stage of disease, bodyweight, etc.).

Mildly hyperglycaemic patients should preferably be treated with metformin, acarbose or thiazolidinediones (which are not associated with any hypoglycaemic risk), while more severely hyperglycaemic individuals should receive a sulphonylurea. In moderately hyperglycaemic patients, sulphonylureas should be preferred in nonobese patients while metformin, and probably also thiazolidinediones, should have priority in obese insulin-resistant type 2 diabetic patients.

Acarbose is mainly indicated to reduce post-prandial glucose fluctuations and improve glycaemic stability. Each antihyperglycaemic agent may also be combined with insulin therapy to improve glycaemic control and/or reduce the insulin requirement of diabetic patients after secondary failure to oral treatment. Finally, safety should be taken into account in elderly patients and/or those with renal impairment, especially as far as the use of sulphonylureas (higher risk of hypoglycaemia) and metformin (higher risk of lactic acidosis) is concerned.

Type 2 diabetes mellitus (formerly known as non–insulin-dependent diabetes mellitus or NIDDM)[1] is a heterogeneous condition caused by both genetic and environmental factors, in which hyperglycaemia results from a dynamic interaction between defects in insulin secretion and insulin action.[2] Various oral antihyperglycaemic agents have been developed over the past 40 years: first sulphonylureas and biguanides and, more recently, α-glucosidase inhibitors and thiazolidinediones.[3-6] Thus, in patients with type 2 diabetes as in those with arterial hypertension, the question of the best choice of first-line drug becomes crucial and stepwise therapy should be recommended if there is failure after initial treatment.

The criteria for drug selection in daily practice should include not only the patient's clinical characteristics (stage of the disease as reflected by the degree of hyperglycaemia, bodyweight, age, renal function, etc.), but also the pharmacological properties of the various compounds available (mode of action, adverse effects, safety profile).[3-6] Knowledge by the physician/practitioner of these latter characteristics may help guide the choice of initial drug treatment for a given patient with type 2 diabetes when diet and exercise fail to maintain adequate glycaemia; similarly, at a later stage of the disease, this knowledge also may help in the decision as to how to best optimise combined drug therapy.[7,8] Updated recommendations for the management of type 2 diabetes mellitus have been published recently by the European NIDDM Policy Group[9,10] and by a consensus panel of the American Diabetes Association.[11]

1. Oral Antihyperglycaemic Agents

Currently available oral antihyperglycaemic agents include sulphonylureas, biguanides (metformin), α-glucosidase inhibitors (acarbose) and thiazolidinediones (troglitazone) [table I].[3-6] These agents, which exhibit different modes of action, (fig. 1) may be used as monotherapy or in various combinations.[12] However, the new compounds acarbose and troglitazone are more expensive than the standard sulphonylurea and biguanide agents.[12] It is noteworthy that none of these oral antihyperglycaemic drugs can be used during pregnancy (women with known type 2 diabetes or with gestational diabetes), except perhaps acarbose which is almost entirely unabsorbed from the gastrointestinal tract.[4]

1.1 Sulphonylureas

Sulphonylureas remain the most popular and inexpensive drug treatment for type 2 diabetes and numerous compounds are available in most countries (table I). These agents essentially stimulate insulin secretion, although some extrapancreatic effects have also been described.[13-15] They appear to be a rational choice to begin pharmacological

Table I. Commercially available oral antihyperglycaemic drugs

Sulphonylureas
first generation
carbutamide, tolazamide, tolbutamide, chlorpropamide
second generation
glibenclamide (glyburide), glipizide (conventional and extended release), gliclazide, gliquidone, glimepiride, etc.
Biguanides
metformin, phenformin[a]
α-Glucosidase inhibitors
acarbose
Thiazolidionediones
troglitazone

a No longer commercially available in most countries.

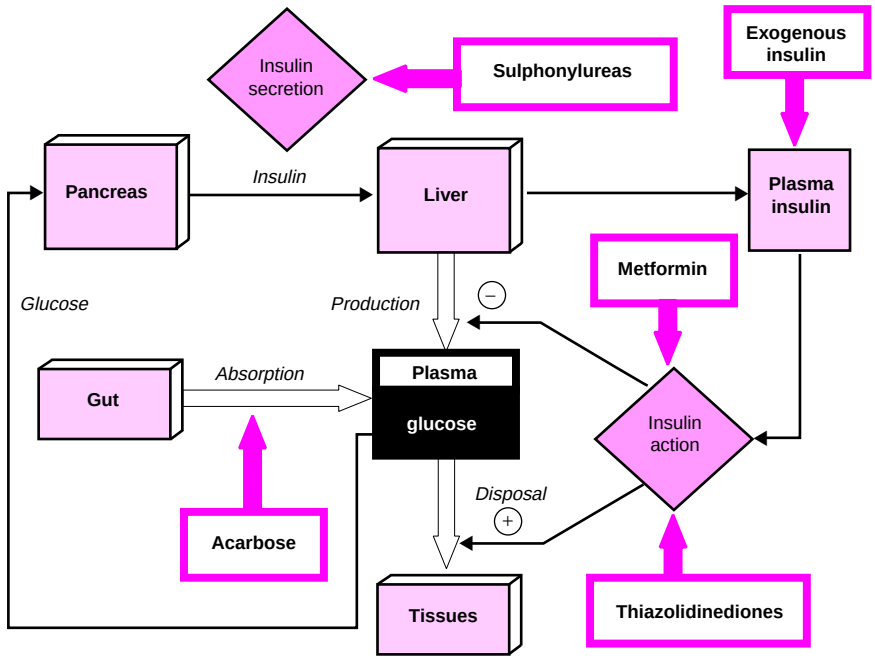

Fig. 1. Current status of oral drug treatment of type 2 diabetes: sites of action of sulphonylureas, metformin, acarbose and thiazolidinediones.

intervention because almost all patients with type 2 diabetes are relatively insulin deficient.[2] However, at best, 60 to 70% of diabetic patients might achieve 'good' glycaemic targets and those with high fasting blood glucose levels and severe obesity rarely achieve desired results. In addition to the rather high initial failure rate, about 10% of patients per year will fail to respond to subsequent therapy.[13-15]

Hypoglycaemia is the main adverse effect of sulphonylurea derivatives, especially in the elderly (see section 2.3 below).[16] Hypoglycaemic episodes appear to be more often associated with chlorpropamide and glibenclamide (glyburide),[17,18] although all sulphonylureas can induce such an adverse effect. Sulphonylurea-induced hypoglycaemic episodes occur mainly in mildly to moderately hyperglycaemic patients receiving too high a dosage as initial therapy, or in whom the dosage is too rapidly increased to control hyperglycaemia.[17,18] Bodyweight gain, sometimes of several kilograms, usually occurs with sulphonylureas, and is undesirable in already overweight patients.[19,20]

Various sulphonylureas are currently available in most countries (table I).[4,14,15] In general, second-generation drugs of this class (glibenclamide, glipizide, gliclazide, gliquidone, glimepiride) are now preferred to first-generation compounds. Extended release glipizide and glimepiride are once-daily preparations which may increase patient compliance with drug therapy. Gliquidone, which is not excreted via the kidneys, may be preferred in patients with mild renal impairment, while glibenclamide should be avoided in such patients because of the higher risk of hypoglycaemia. In general, near-maximal sulphonylurea-induced antihyperglycaemic effect can be achieved with extended release glipizide 5mg or glimepiride 4mg once daily, or with glibenclamide 5mg, conven-

tional glipizide 5 to 10mg, gliclazide 80mg or gliquidone 30mg twice (occasionally 3 times) daily. In most cases, initial dosages should be reduced by at least half to avoid hypoglycaemia, especially in only mildly to moderately hyperglycaemic diabetic patients. Some studies have suggested that taking the sulphonylurea compound 30 minutes before a meal may help to control early postprandial hyperglycaemia.

1.2 Metformin

The glucose-lowering effect of the biguanide compound metformin does not depend on the stimulation of insulin secretion but, rather, is attributed to enhanced non–insulin-mediated and insulin-mediated glucose metabolism. The underlying mechanisms are still unclear but metformin has been shown to decrease hepatic glucose output, stimulate peripheral glucose uptake and increase intestinal glucose use.[21-26]

Insulin resistance is a key feature of type 2 diabetes, especially when obesity is present,[2] and represents a major target in the treatment of the disease.[27,28] As metformin can improve insulin sensitivity and reduce hyperinsulinaemia, it would be more appropriate as a first-line antidiabetic drug in obese diabetic patients.[7-11] The UK Prospective Diabetes Study (UKPDS) has reported that the improvement of glycaemic control obtained with metformin is similar to that obtained with sulphonylureas or insulin in newly diagnosed obese diabetic patients.[19,20] Another interesting effect of metformin is its favourable action on various disorders associated with insulin resistance, such as high triglyceride levels, low levels of high-density lipoprotein (HDL) and high plasminogen activator inhibitor-1 (PAI-1) levels, frequently seen in obese subjects, with or without type 2 diabetes.[25,29] Hence, diabetic patients who also exhibit the insulin resistance syndrome may be good candidates for metformin therapy.

The dosage of metformin should be increased progressively, from a starting dose of 500 to 850mg to a maximum dosage averaging 1500 to 2500 mg/day. In order to improve digestive tolerance, it is also recommended that the drug be taken during meals. Nevertheless, gastrointestinal adverse effects may hinder the use of metformin in some patients.[23] In contrast to the sulphonylureas, metformin does not cause bodyweight gain, [19,30] reduces rather than increases plasma insulin levels and only rarely causes overt hypoglycaemia.

Lactic acidosis remains the major potential adverse effect of biguanide therapy.[31] Two compounds, buformin and phenformin, are not marketed anymore because of this serious complication. In contrast, lactic acidosis is rare with metformin and the drug is well tolerated if it is avoided in patients with contraindications to its use, i.e. any person with decreased renal function, liver disease and cardiac or respiratory insufficiency.[31] Its use in the elderly remains controversial and is subject to individual clinical judgement (see below in section 2.3).[32,33]

1.3 α-Glucosidase Inhibitors

α-Glucosidase inhibitors such as acarbose exert a competitive, dose-dependent inhibition of small intestinal α-glucosidase enzymes which break down nonabsorbable complex carbohydrates into absorbable monosaccharides.[34-38] Such action leads to a delayed and reduced rise in postprandial blood glucose levels, and consequently plasma insulin concentrations.

Several studies have shown that acarbose improves indices of blood glucose stability in type 2 diabetic patients treated with diet, oral hypoglycaemic agents or insulin.[34-38] Improvement of glycated haemoglobin (HbA_{1c}) levels was obtained with no increase, or even a reduction, in bodyweight and the incidence of hypoglycaemic episodes.[34-38]

As acarbose is not absorbed, no systemic adverse effects are expected. The major adverse effect of α-glucosidase inhibitors is gastrointestinal intolerance (flatulence, soft stools or diarrhoea, mild abdominal pain), due to both osmotic effect and bacterial fermentation of undigested carbohydrates in the distal bowel. Many of these symptoms are dose-related and transient. Thus, acarbose dos-

age should be increased very slowly (beginning with 25 to 50mg once daily) and adjusted in each patient individually (by increasing the dosage by 50 mg/day every week, up to 50 to 100mg 3 times daily) in order to limit gastrointestinal symptoms and improve compliance.[34-38]

1.4 Thiazolidinediones

Thiazolidinediones are a new class of compounds which work by enhancing insulin action and thus promote glucose utilisation in peripheral tissues, possibly by stimulating nonoxidative glucose metabolism in muscle, and suppressing gluconeogenesis in the liver. They have no effect on insulin secretion and are known as 'insulin sensitisers'.[39-41] This action is attributed to the stimulation of a new class of nuclear receptors, peroxisome proliferative activated receptors (PPAR-γ), which enhance the expression of a number of genes encoding proteins involved in glucose and lipid metabolism.[40,41]

Troglitazone[42,43] (like other thiazolidinediones in clinical development) has been shown to improve insulin resistance and glucose tolerance in obese subjects with impaired glucose tolerance as well as in nonobese (mainly Japanese) or obese (mainly American or European) patients with type 2 diabetes, without inducing bodyweight gain or drug-related hypoglycaemia.[44,45] Interestingly enough, several components of the insulin resistance syndrome, e.g. lipid abnormalities and arterial hypertension, also appeared to be improved by troglitazone.[46] Antioxidant effects have also been described.[41] In a study planned to exclude the cardiac adverse effects of troglitazone, type 2 diabetic patients treated with the drug for more than 2 years seemed to have benefited from enhanced cardiac output and stroke volume, possibly secondary to decreases in mean arterial pressure and peripheral vascular resistance.[47] Troglitazone seems to be devoid of severe adverse effects at the dosages used (200 to 600mg once daily), although mild anaemia has been reported.[41-43]

The time course of onset of action of thiazolidinediones can be variable but seems to be slower than that of other antihyperglycaemic agents: it generally requires 1 to 4 weeks of therapy with troglitazone for initial plasma glucose- and insulin-lowering effects, with maximal responses (mean reduction of 20% in plasma glucose concentrations and of 30% in plasma insulin levels) after 6 to 8 weeks. Most studies have indicated that a daily dose of troglitazone 400mg is more efficacious than one of 200mg, and some have suggested an even greater effect with a daily dose of 600mg. An intriguing aspect of troglitazone therapy is the fact that some patients with type 2 diabetes (about 20 to 30%) fail to respond to the drug when it is either given as monotherapy or added to the regimens of patients who have had unsatisfactory responses to sulphonylureas. As yet, no common metabolic variables have been identified to indicate which patients are likely to be nonresponders.[41]

2. Therapeutic Strategy in Type 2 Diabetes

2.1 First Choice Drug Treatment

After diet failure, patients with type 2 diabetes can be treated with one of the 4 available oral antihyperglycaemic drugs before considering the use of insulin (figs 1 and 2).[7-11] It is conventional wisdom that metformin should be preferred in obese patients while sulphonylureas should be prescribed first in nonobese or only modestly overweight individuals.[7-11] This recommendation is based on the fact that obese people are often hyperinsulinaemic (and thus do not apparently require further sulphonylurea-induced stimulation of insulin secretion), while at the same time, are insulin-resistant, and that metformin (in contrast to the sulphonylureas) does not promote bodyweight gain.[21-26] Another advantage of prescribing metformin first in obese diabetic patients is that it can favourably influence the metabolic abnormalities frequently associated with insulin resistance.[29,48] However, recent studies have suggested that metformin may be as effective in nonobese diabetic patients as in the obese.[49]

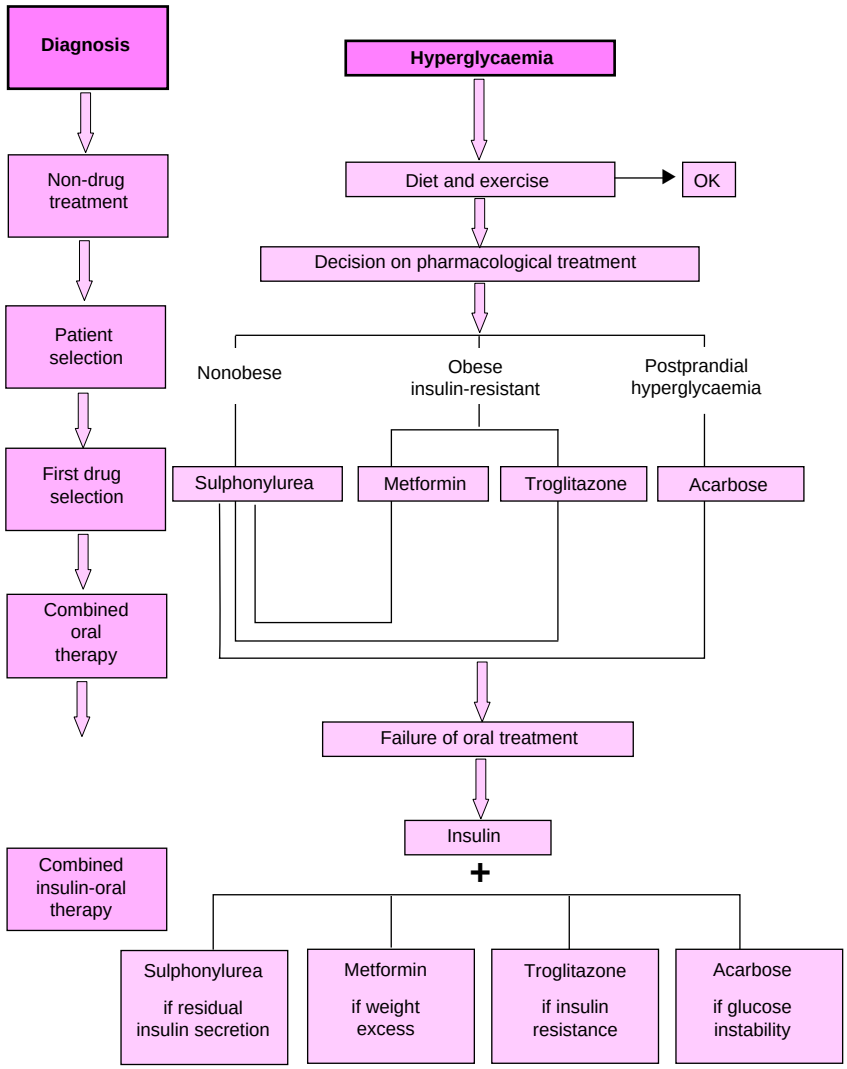

Fig. 2. Stepwise treatment of type 2 diabetes: a guide to the selection of oral antihyperglycaemic agents. In most cases, when combination therapy is considered, either metformin, troglitazone or acarbose, depending on whether the patient is obese, insulin-resistant or postprandial hyperglycaemic, is added to a sulphonylurea. Other combinations can also be considered but have not yet been extensively studied (see section 2.2).

In patients without significant bodyweight excess, it is generally considered that the role of deficient insulin secretion is predominant.[2] Consequently, the use of drugs able to stimulate pancreatic islet β-cells seems to be most appropriate.[10] Such treatment with a sulphonylurea compound undoubtedly can improve glycaemic control in many patients; however, it still remains unclear whether it can influence the natural history of the disease. Because of the fairly high rate of secondary failure to sulphonylureas,[50] it has been suggested that such compounds may accelerate the exhaustion of islet β-cells. This remains, however, a matter of controversy.

Acarbose appears to be preferable as monotherapy in type 2 diabetic patients with only modest fasting hyperglycaemia but somewhat high postprandial glucose excursions.[10,11] In such patients, acarbose can improve glycaemic control without inducing hypoglycaemia. A specific place of acarbose in the treatment of the elderly patient may also be considered (see section 2.3 below). The place of the recently developed compound troglitazone in the general treatment strategy for type 2 diabetes has not been considered in the European[10] or American guidelines[11] and remains to be more precisely specified.[12] Owing to its mode of action, troglitazone should be preferred in insulin-resistant patients. Apparently, it has the same profile of action as metformin.[51] In contrast to metformin however, troglitazone does not induce gastrointestinal adverse effects and can be used in the elderly and in the presence of renal insufficiency without risk of lactic acidosis.

Short term studies on small groups of patients have suggested that the different oral hypoglycaemic agents are almost all equally effective in decreasing HbA_{1c} levels. Such was the case in clinical trials comparing sulphonylureas versus metformin,[52] sulphonylureas versus acarbose,[53] metformin versus acarbose,[54] troglitazone versus sulphonylureas[47] and troglitazone versus metformin.[51] Unfortunately, long term studies are very scarce and, in this respect, the available results of the UKPDS are interesting.[19,20] They showed that both sulphonylureas and metformin are as effective as insulin in controlling fasting plasma glucose concentrations and HbA_{1c} levels during the first 3 years, and were significantly superior to diet therapy alone. One advantage of metformin in the obese group of diabetic patients was the absence of bodyweight gain, which contrasted with a significant bodyweight increase in the group treated with sulphonylureas or insulin. Unfortunately, at the present time, it is not known which is the best treatment to retard the progression of the disease and to prevent diabetic complications; the final results of the UKPDS are awaited with increasing interest.

Attempts to compare the risks of the two most prescribed classes of oral antidiabetic agents have also been reported.[55,56] It was concluded that the risk of developing lactic acidosis on metformin is less likely than that of developing severe hypoglycaemia on sulphonylurea therapy. However, it is difficult to draw any definite conclusion from such population surveys as the individual risk essentially depends on the type of patient, the dose of medication and the recommendations for proper use. As far as acarbose is concerned, no severe adverse effects have been reported as yet.

Although troglitazone was considered a well-tolerated drug during clinical trials, about 40 cases of serious hepatic dysfunction have been reported spontaneously since its launch (to date, approximately 800 000 patients have been prescribed troglitazone in the US and Japan), including, rarely, severe hepatocellular damage, hepatic necrosis and hepatic failure. One patient died of hepatic failure and another required liver transplantation.[57] Many of the cases are poorly documented and have multiple contributing factors. However, it is not possible to exclude troglitazone as a causal factor. Therefore, troglitazone should be discontinued in the presence of unexplained deterioration of hepatic function and in all patients liver function should be checked periodically.

Several drug interactions have been noted with antihyperglycaemic drugs, those of clinical importance being mainly described with the sulphonylureas.[58] However, these drug interactions rarely represent a criterion for the selection or exclusion of an oral blood glucose–lowering agent.

From a practical point of view, the selection of an oral agent for initial drug therapy is made easier by considering the stage of the disease, i.e. the level of glycaemic control. Patients with a fasting plasma glucose level of less than 7.8 mmol/L (140 mg/dl) are best treated with the agents that are not likely to cause hypoglycaemia: metformin may be preferred in patients with mainly fasting hyperglycaemia, acarbose in those with prominent postprandial hyperglycaemia and troglitazone in those with severe insulin resistance.[12] In this respect, it

may not be a simple coincidence that new criteria for diabetes [fasting plasma glucose levels >7 mmol/L (126 mg/dl) instead of >7.8 mmol/L (140 mg/dl)] have recently been published,[1] at a time when new antihyperglycaemic agents such as metformin, acarbose and troglitazone have become available on the US market. Patients beginning treatment at intermediate levels of fasting plasma glucose between 7.8 and 11.1 mmol/l (140 and 200 mg/dl, respectively) are best treated with low doses of sulphonylureas if they are only mildly to moderately overweight, or preferably with metformin if they are more obese. Finally, in severely hyperglycaemic patients [fasting plasma glucose exceeding 11.1 mmol/L (200 mg/dl)], patients are most reliably and economically treated with a sulphonylurea in the first instance; metformin may be an alternative choice in very obese patients.[12]

2.2 Combined Therapy

As the 4 classes of antihyperglycaemic drugs currently available (sulphonylureas, biguanides, α-glucosidase inhibitors and thiazolidinediones) have different modes and sites of action (fig. 1), they may be combined in a stepwise fashion to provide more ideal glycaemic control for most patients.[7-12,59]

The most common combined therapy associates sulphonylureas and metformin.[52,60] Numerous studies have demonstrated that both compounds have an additive antihyperglycaemic effect, without increasing the adverse effects of either pharmacological class. Other combinations of oral drugs may also be used,[7-12] especially by considering acarbose and troglitazone, even if the cost of these 2 compounds is clearly higher than that of sulphonylureas or metformin. Acarbose has been associated successfully with sulphonylureas[61-63] and such a combination was shown to be as effective as the standard sulphonylurea-metformin association.[64] Acarbose use in combination with metformin has also be proven to be effective,[62,65] even though a short term pharmacokinetic study in healthy volunteers showed that it could reduce the bioavailability of metformin by around 35%.[66]

In a large, randomised, placebo-controlled study performed in Japan, troglitazone appeared to be a useful antihyperglycaemic agent in the combined treatment of patients with type 2 diabetes who were not well controlled by sulphonylureas alone.[67] A preliminary study demonstrated that the combination of troglitazone and metformin was well tolerated and had additive effects on fasting plasma glucose and HbA_{1c} levels, as well as on insulin-mediated glucose disposal in obese diabetic patients.[51] To our knowledge, the combination of troglitazone with acarbose has not yet been evaluated.

Greater knowledge of the pathophysiology of type 2 diabetes[2] and of the modes of action of oral antidiabetic drugs[3-6] provided the theoretical basis for the renewed interest in combining insulin with oral drugs after secondary failure of oral treatment.[68] However, the characteristics of patients who would get the most benefit from such combined treatment are not yet fully defined (fig. 2).

The insulin-sulphonylurea combination has been the most extensively studied.[69] It has been demonstrated that the persistence of a significant endogenous secretion of insulin is a prerequisite to take advantage of such a combination.[70,71] Metformin may be used in combination with insulin to reduce the requirement for the latter in obese patients,[72] to improve glycaemic control and/or to correct associated metabolic abnormalities.[73] Favourable results from troglitazone 200 to 600 mg/day on both glycaemic control and insulin need have been obtained in 2 recent large multicentre, placebo-controlled studies performed in type 2 diabetic patients who were poorly controlled (HbA_{1c} levels >8.5%) despite multiple insulin injections of more than 30 U/day (cited in Henry[41]). Acarbose may be added to insulin to reduce blood glucose variations, especially postprandial early hyperglycaemia and late hypoglycaemia.[74-75]

The cost/benefit ratio of combined therapy remains, however, to be assessed in large randomised trials, as does the question whether better metabolic control may be maintained in the long term with combination therapy compared with monotherapy.

2.3 Elderly Patients with Type 2 Diabetes

As the prevalence of type 2 diabetes and the risk of severe adverse effects of oral antihyperglycaemic agents are markedly increased with aging, there should be special focus on the specific group of elderly diabetic patients.[32,33] In general, the same measures of management are appropriate in the older patient with diabetes as in the younger, but they may need to be modified in the presence of comorbidities, polymedication or social isolation.

Prolonged hypoglycaemia represents the most common and severe adverse effect of sulphonylureas. It occurs more frequently in the elderly and can lead to permanent neurological damage and death.[14] If a sulphonylurea compound should be prescribed in an older diabetic patient, drug treatment must start with very low doses and the dosage must be increased with caution.[32] Most severe and prolonged hypoglycaemic episodes have been described with the sulphonylurea compound glibenclamide, which should probably be avoided in this specific population.[17,18]

Because most cases of lactic acidosis have been reported in elderly patients,[31] metformin is usually not recommended in individuals over the age of 65 to 70 years.[9,32] If metformin is to be used in any elderly diabetic patient, he/she must have normal renal and hepatic function tests and be free of significant cardiovascular or pulmonary disease. Moreover, renal function should be checked routinely and the biguanide must be stopped if a deterioration in renal function is observed. Furthermore, metformin should be stopped if a patient is being treated with a nephrotoxic medication, is undergoing a dye study or develops a significant acute illness. Provided that these precautions are taken, the risk of metformin-induced lactic acidosis seems to be very low, even in the elderly population.[76-80]

Despite the fact that few data are available on the therapeutic use of this drug in the elderly,[36,61] α-glucosidase inhibitors such as acarbose have been recommended, in preference to sulphonylureas or biguanides, as first-line treatment on theoretical grounds of mechanism of action for patients with mild hyperglycaemia who might be at risk of hypoglycaemia or lactic acidosis.[34] No studies with troglitazone have been specifically devoted to the elderly. However, patients older than 65 years have been included in several clinical trials and no particular adverse effects were reported. Thus, thiazolidinediones appear to be as well tolerated in elderly diabetic individuals as in younger patients.[41-43]

3. Conclusions

While sulphonylurea compounds have been the only oral antihyperglycaemic drugs available for many years in numerous countries, the scene is set to change with the recent introduction of metformin in the US (although this drug has been available for more than 30 years in Europe), the launch of the α-glucosidase inhibitor acarbose in most countries and the recent introduction of the thiazolidinedione compound troglitazone in the US and Japan. All these drugs exert their antihyperglycaemic action via different mechanisms (promoting insulin secretion, enhancing insulin action or delaying intestinal carbohydrate absorption). Several studies have shown that any of the oral antihyperglycaemic agents are as effective as other oral antihyperglycaemic compounds. However, with the exception of the ongoing UKPDS,[19,20] all these clinical trials were fairly short term and performed on quite small groups of patients. Owing to the heterogeneity of type 2 diabetes and the various modes of action of the available antihyperglycaemic drugs, it is reasonable to conclude that one compound could be more effective than another in one individual patient with particular characteristics.

Safety considerations should also be taken into account in elderly patients in whom the use of sulphonylureas and metformin may lead to severe adverse effects occurring at a higher rate. Considering the high prevalence of type 2 diabetes in the older populations, the potential advantages of acarbose and troglitazone should be evaluated

more closely in elderly patients. As is the case with hypertension, the increasing numbers of different drugs available will probably favour the use of combined therapy, although it remains to be established which combination will provide the best results in a given diabetic patient. Finally, it is noteworthy that, until now, no long term studies in type 2 diabetic patients have demonstrated that any kind of antihyperglycaemic oral agent helps to postpone or prevent micro- or macroangiopathic complications.[81]

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Errata

Vol. 54, No. 6, page 895: In table IV, the fourth column [Mean baseline seated SBP/DBP (mm Hg)], rows 1 and 2 should read (in descending order) *155/101, 155/100*.
page 895: In table IV, the fifth column [Mean decrease from baseline in trough seated SBP/DBP (mm Hg)], rows 1 to 4 should read (in descending order) *12/10, 16/12, 11/9, 4/5*.
page 896: In column 1, line 6 should read, '. . . versus *63%* of enalapril . . .'.
page 896: In column 2, line 4 should read, '. . . monotherapy (*9* and *7%* . . .'.
page 901: Reference no. 39 should read, 'Kassler-Taub K, *Littlejohn T, Elliott W, et al. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild-to-moderate hypertension. Am J Hypertens. In press*'.

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